REMARKS

In response to the Office Action of June 28, 2007, claims 1, 4, 9 and 10 are hereby amended, claims 11 and 12 are canceled and new claims 13-17 are added. Support for the amendments to claims 1 and 9 can be found throughout the Specification; see for example paragraphs 6, 9, 10, 40 and 51 which generally describe the method of the invention. Support for new claims 13, 16 and 17 can be found in paragraph 26, which lists "antibody fragments" and "nucleic acid ligands" as potential captures reagents. Support for the amendments to claim 10, as well as new claims 14 and 15 can be found in paragraph 34, which describes the use of Universal Protein Stains as a means of detection of protein analytes.

Claims 1, 2, 4 and 11 were rejected under 35 U.S.C. § 102(b); claims 1 and 3-12 were rejected under 35 U.S.C. § 103(a) and claims 5-8 were rejected under 35 U.S.C. §§ 102(b)/103(a). Each of these rejections is discussed below.

Rejection Under 35 U.S.C. § 102

The Court of Appeals for the Federal Circuit has stated that anticipation requires the presence in a single prior art reference of each and every element of the claimed invention. *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1458 (Fed. Cir. 1984); *Alco Standard Corp. v. Tennessee Valley Auth.*, 1 U.S.P.Q.2d 1337, 1341 (Fed. Cir. 1986). "There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention." *Scripps Clinic v. Genentech Inc.*, 18 U.S.P.Q.2d 1001, 1010 (Fed. Cir. 1991) (citations omitted).

The Examiner has maintained the rejection of claims 1, 2, 4 and 11 under 35 U.S.C. § 102 (b) as being anticipated by Graham *et al.* (U.S. Pat No. 4,743,452) for the reasons of record. In Applicant's Amendment and Remarks document filed on April 12, 2007, Applicant took the position that Graham *et al.* teach a method for reducing the "hook effect" in antibody-based sandwich type immunoassays and that unlike the method of the instant invention Graham *et al.* do not teach or suggest that their method can be extended to a sample containing a mixture of analytes, to a non-sandwich based assay or

to a non-antibody based assay. In rejecting this argument, the Examiner reasons that the features upon which Applicant relies are not recited in the rejected claims and that a preamble is generally not accorded any patentable weight. In response, independent claim 1 has been amended to clarify the instant invention is drawn to a method for detecting a mixture of analytes and claim 11 has been canceled.

Graham *et al.* teach a method for reducing the "hook effect" in antibody-based sandwich type immunoassays. As provided in the Specification, the hook effect results from the first and second binding partners in a sandwich based assay being bound to different analytes. As a result, fewer sandwich complexes are formed giving a false lower concentration of ligand than is actually present in the sample (Graham *et al.* col. 2, lines 3-12). Thus the hook effect is a phenomenon which is particular to sandwich-based assays. The immunoassays disclosed by Graham *et al.* comprise a first ligand binding partner which is immobilized on a solid support and then reacted --thereby potentially forming a sandwich complex-- with a second ligand binding partner in accordance with the presence or absence of the ligand/analyte to be detected. To reduce the hook effect either the first ligand binding partner or the second ligand binding partner or a combination thereof is added in excess. As taught and claimed the method is specific for antibody-based sandwich type immunoassays for use in the quantification of a single analyte (ligand). The reference does not teach or suggest that the method can be extended to a sample containing a mixture of analytes, to a non-sandwich based assay or to a non-antibody based assay.

The present invention on the other hand is drawn to a method for simultaneously quantifying high and low abundance analytes that may be contained in a biological sample. (Specification, paragraph 1). As noted in the background section of the invention, prior to the filing of the instant application, "protein levels [were] measured individually with assays tailored to each analyte of interest." (Specification, paragraph 3). Thus, one objective of the instant invention as set forth in paragraph 5 of the Specification was "to provide a general method for adjusting the inherent quantification range of a particular set of analytes to higher concentration regions, leaving the range of the remaining analytes the same and thereby permitting the simultaneous and accurate

quantification of a plurality of analytes over a wide range of concentration values." The present invention provides for the first time a method for analyzing simultaneously a potentially complex mixture of analytes using a non-sandwich based assay.

Referring to the claims, independent claim 1, as amended, is drawn to a method for detecting the amount of a first analyte in a biological fluid without decreasing the amount of a second analyte in said biological fluid. The method comprises a) providing a first quantity of the first capture reagent and a first quantity of the second capture reagent wherein said first quantity of the first and second capture reagents are immobilized on a solid support; b) contacting the solid support with a mixture comprising said biological fluid and a second quantity of said first capture reagent, wherein the amount of the first analyte is decreased without decreasing the amount of the second analyte; and c) detecting the amount of said first analyte via its binding to said first capture reagent immobilized to said solid support. As provided in the Specification, "the addition of a quantity of the first capture reagent free in solution quantitatively specifically titrates the amount of the first analyte captured in the assay, lowering saturating levels of the first analyte to quantifiable levels," without affecting the concentration other analytes present in the sample" (Specification, paragraph 6). Thus, as amended, claim 1 clarifies that the method of the instant invention is drawn to the detection and quantification of more than one analyte (step b) and is a non-sandwich based assay (step c) (only one capture reagent per analyte is employed in the method). In contrast, as noted above, Graham *et al.* teach a method for quantifying a single analyte in a sample using a sandwich based immunoassay, involving two capture reagents, only one of which is immobilized on the solid support. Thus, Applicant maintains that this reference neither teaches nor suggests the method of the instant invention as set forth in claim 1, as amended, and as such respectfully requests that this rejection be withdrawn.

The Examiner has maintained the rejection of 1, 2, 4 and 11 under 35 U.S.C. § 102(b) as being anticipated by Neumann *et al.* (U.S. Pat No. 6,184,042) for the reasons of record. In Applicant's Amendment and Remarks document filed on April 12, 2007, Applicant took the position that Neumann *et al.*, like Graham *et al.* teach a method for reducing the "hook effect" in antibody-based sandwich type immunoassays for use in

quantification of a single analyte (ligand). In rejecting this argument, the Examiner reasons that the features upon which Applicant relies are not recited in the rejected claims. For the reasons discussed above with respect to the Graham *et al.* reference, Applicant maintains that this reference does not teach or suggest the method of claims 1, 2 and 4 of the instant invention as amended. Applicant therefore respectfully requests that this rejection be withdrawn.

The Examiner has maintained the rejection of claims 1, 2, 4 and 11 under 35 U.S.C. § 102(b) as being anticipated by Piasio *al.* (U.S. Pat No. 4,098,876) for the reasons of record. In Applicant's Amendment and Remarks document filed on April 12, 2007, Applicant took the position that Piasio *et al.* teach an improved method for performing an antibody based sandwich assay, which is specific for sandwich type antibody-based immunoassays for use in quantification of a single analyte (ligand). In rejecting this argument, the Examiner again reasons that the features upon which Applicant relies are not recited in the rejected claims. For the reasons discussed above with respect to the Graham *et al.* reference, Applicant maintains that this reference does not teach or suggest the method of claims 1, 2 and 4 of the instant invention as amended. Applicant therefore respectfully requests that this rejection be withdrawn.

Rejections under 35 U.S.C. § 103(a)

The Examiner bears the burden of establishing a prima facie case of obviousness. In determining obviousness, one must focus on Applicant's invention as a whole. *Symbol Technologies Inc. v. Opticon Inc.*, 19 USPQ2d 1241, 1246 (Fed. Cir. 1991). The primary inquiry is:

> whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have had a reasonable likelihood of success. . . . Both the suggestion and the expectation of success must be found in the prior art, not in the applicant's disclosure.
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> *In re Dow Chemical*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988).

The Examiner has maintained the rejection of claims 1 and 3-12 under 35 U.S.C. § 103(a) as being unpatentable over Lin *et al.* (US 2002/0037506) in view of Graham *et al.* (U.S. Pat No. 4,743,452) or Neumann *et al.* (U.S. Pat No. 6,184,042) for the reasons

of record. In response to this rejection, independent claims 1, 9 and 10 have been amended, and claims 11 and 12 have been canceled.

As noted above, the present invention is drawn to a method for simultaneously quantifying high and low abundance analytes that may be contained in a biological sample. Independent claim 1, as amended, is drawn to a method for decreasing the amount of a first analyte in a biological fluid that is capable of binding to a first capture reagent immobilized on a solid support without decreasing the amount of a second analyte in said biological fluid. As noted above, the method comprises a) providing a first quantity of the first capture reagent and a first quantity of the second capture reagent wherein said first quantity of the first and second capture reagents are immobilized on a solid support; b) contacting the solid support with a mixture comprising said biological fluid and a second quantity of said first capture reagent, wherein the amount of the first analyte is decreased without decreasing the amount of the second analyte; and c) detecting the amount of said first analyte via its binding to said first capture reagent immobilized to said solid support. Thus, as amended, claim 1 clarifies that the method of the instant invention is drawn to the detection and quantification of more than one analyte (step b) and is a non-sandwich based assay (step c) (only one capture reagent per analyte is employed in the method).

Lin *et al.* teach an aptamer based two-site binding sandwich assay employing nucleic acid ligands rather than antibodies as the capture agents. The immunoassays disclosed by Lin *et al.* comprise a first capture molecule which is immobilized on a solid support and then reacted --thereby potentially forming a sandwich complex-- with a second capture molecule (reporter molecule) in accordance with the presence or absence of the ligand/analyte to be detected (Specification, page 3, paragraph14). As described in paragraph 14, "said capture molecule and the reporter molecule both are a nucleic acid ligand to said target molecule." The method can be used to perform multiplexed analysis of a mixture of targets proteins (Specification, page 1, paragraph 2). Unlike the method of the instant invention however, Lin *et al.* do not teach or suggest the addition of capture reagent free in solution as a means to specifically lower saturating levels of one analyte to

quantifiable levels without decreasing the amount of a second analyte. Nor does Lin *et al.* teach or suggest a non-sandwich based assay.

As noted above, both Graham *et al.* and Neumann *et al.* teach immunoassays for use in quantification of a single analyte (ligand). Thus, as in the case of Lin *et al.* neither one of these references teach or suggest the addition of capture reagent free in solution as a means of lowering the concentration of one analyte to quantifiable levels without decreasing the amount of a second analyte. Additionally, both Graham *et al.* and Neumann *et al.* teach a method for reducing the "hook effect" in antibody-based sandwich type immunoassays. As noted above, the hook effect results when the first and second binding partners in a sandwich based assay bind to different analyte and as such is a phenomenon which is particular to sandwich-based assays. Thus, with reference to Graham *et al.*, the immunoassay illustrated comprises "a first HCG specific binding partner . . . labeled with a hapten . . . and a second HCG binding partner . . . labeled with an enzyme." (col. 3, lines 43-46). Likewise, with reference to Newmann *et al.*, the immunoassay comprises: incubating "a sample containing an analyte to be determined . . . with a first receptor, second receptor and solid phase in an arbitrary order in order to ensure that an immobilized sandwich complex forms." (col. 4, lines 45-50). Thus, as in the case of Lin *et al.* both each of these references employ the use of two capture agents in a sandwich based assay. Thus, neither of these references cure the defects noted in the Lin *et al.* reference. As such, Applicant maintains that this combination of references does not render the method of independent claim 1 and dependent claims 3-8 and 13-15 obvious. Applicant therefore respectfully requests that the Examiner reconsider this rejection.

Independent claim 9, as amended, is drawn to a method for increasing saturation point for a first analyte of a first capture reagent immobilized on a solid support, without decreasing the saturation point for a second analyte of a second capture reagent immobilized on said solid support in a measurement wherein the level of the first analyte is detected via its binding to the first capture agent immobilized to said solid support. The method comprises contacting said solid support with said first capture reagent free in solution. Thus, as amended, claim 9 clarifies that the method is drawn to the detection of

more than one analyte and is a non-sandwich assay (only one capture reagent per analyte is employed). As such, Applicant maintains for the reasons set forth above, that this combination of references does not render the method of independent claim 9, as amended and dependent claims 16 and 17 obvious. Applicant therefore respectfully requests that the Examiner reconsider this rejection.

Independent claim 10 has been amended to include the use of a universal protein stain as a means of detection. None of the references relied upon by the Examiner either teach or suggest this method of detection. As such, Applicant maintains that independent claim 10 is not rendered obvious by this combination of references and respectfully requests that the Examiner withdraw this rejection.

Rejections under 35 U.S.C. § 102(b)/103(a)

The Examiner has maintained the rejection of claims 5-8 under 35 U.S.C. § 102(b) as being anticipated by, or in the alternative under 35 U.S.C. § 103(a) as being obvious over Graham *et al.* (U.S. Pat No. 4,743,452) or Neumann *et al.* (U.S. Pat No. 6,184,042) or Piasio *et al.* (U.S. Pat No. 4,098,876). As discussed above in detail each of the references relied upon by the Examiner teach a method for performing antibody-based sandwich type immunoassays for use in quantifying a single analyte in a sample. Claims 5-8 of the instant invention depend from claim 1, which as amended is drawn to a method for decreasing the amount of a first analyte in a biological fluid that is capable of binding to a first capture reagent immobilized on a solid support without decreasing the amount of a second analyte in said biological fluid. Thus, claim 1, as amended, is drawn to a method for decreasing the concentration of one analyte in a sample comprised of a mixture of analytes using a non-sandwich based assay. In contrast, as noted above, each of the references relied upon by the Examiner teach a method which is individually tailored to the analyte of interest using a sandwich based assay. Thus, Applicant maintains that these references neither teach nor suggest the method of the instant invention as set forth in dependent claims 5-8. In light of this Applicant respectfully requests that this rejection be withdrawn.

If it would be helpful to obtain favorable consideration of this case, the Examiner is encouraged to call and discuss this case with the undersigned. This constitutes a request for any needed extension of time and an authorization to charge all fees therefore to deposit account No. 19-5117 if not otherwise specifically requested. The undersigned hereby authorizes the charge of any fees created by the filing of this document or any deficiency of fees submitted herewith to be charged to deposit account No. 19-5117.

Respectfully submitted,

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